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On the role of rostral prefrontal cortex (area 10) in prospective memory

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Introduction

This book is testament to the wonderful advances that have been achieved in the last few years in the field of prospective memory (PM[1]) research. However this is still a very new area of study. Also relatively new are the methods in cognitive neuroscience which enable us to localise the neural underpinnings of specific behavioural functions. So one might expect, at this early scientific stage, that the evidence that links particular brain regions to prospective memory would might be somewhat contradictory. Very surprisingly, however, this is not the case, at least for the frontal lobes. There is a general consensus that the executive functions of the frontal lobes play some part in supporting prospective memory. This comes both from evidence of structural abnormality in the frontal lobes in people with an acquired prospective memory deficit (e.g. Fortin, Godbout and Braum, 2003) or through studies linking executive processing with prospective memory performance (e.g. Kliegel, Eschen and Thone-Otto, 2004; Knight, Titov and Crawford, 2006; Mantyla, 2003; Marsh and Hicks, 1998; McDaniel et al, 1999; Salthouse et al, 2004; but see Matthias and Mansfield, 2005)

Most recently, there is early evidence which suggests a special role for one sub-region of the frontal lobes: area 10. This region is also rather confusingly referred to in the literature as “Brodmann’s Area 10; rostral prefrontal cortex”; “anterior prefrontal cortex”; “frontopolar cortex”; or the “frontal pole”. This is a very interesting brain region: It is very large in humans: in volumetric terms probably the largest single architectonic region of the frontal lobes (Christoff et al, 2001), covering approx. 25-30 cubic cms. (Semendeferi et al, 2001). It is also in relative terms much larger in the human brain than in other animals, including the great apes (Semendeferi et al, 2001; but see Holloway, 2002). Additionally, this region is probably the last to achieve myelination, and it has been argued that tardily myelinating areas engage in complex functions highly related to the organism’s experience (Fuster, 1997, p. 37). These are all good reasons to imagine that the rostral prefrontal cortex may support cognitive processing which is especially important to humans. And very recent evidence seems to suggest that this brain region may play a critical part in the supporting the processes that enable prospective memory. This chapter is a review of the currently available evidence, which comes from two main

sources. The first is lesion evidence; the second is evidence from functional brain imaging.

Area 10 and prospective memory: Human lesion evidence.

Perhaps the easiest way of making a link between the functions of particular brain regions and prospective memory would be to find a series of people with circumscribed cerebral involvement who have either isolated PM impairments (i.e. show *no* impairment on any other kind of test*)*, or show isolated impairments at different stages of remembering to carry out a delayed intention. However to our knowledge this has not yet occurred. Of course this could be because the appropriate patient has not yet been discovered. However it is also possible that this is consistent with a view of prospective memory as a *function* (i.e., behaviourally-defined, directly observable) rather than a *construct* (i.e. a theoretical entity, independent in some way from others), and one that requires the operation of "central" rather than "informationally encapsulated" resources. On this account, many theoretically independent processing resources (e.g. sustained attention, retrospective memory, inhibition, etc.) work together to enable the behaviour called "prospective memory". Consistent with this account is the view that these resources are used to enable other forms of behaviour as well. If this is correct, then a processing impairment which produces a prospective memory deficit will also be likely to cause observable deficits in other functions (see Burgess et al, 2006 for an outline of the distinctions between functions and constructs). Indeed, this is central to the notion of "central processes" and the consequent "low process-behaviour correspondence" in the field of executive functions (Burgess, 1997) – in other words, that executive control processes contribute to a range of different behaviours.

Prima facie, this complicates investigations. However this situation (if true) actually means that examining the symptoms that co-exist with the prospective memory ones, and the situation in which they occur, can give a key insight into the processing components of prospective memory. Indeed, in this way, to study *only* performance on prospective memory tests would be a mistake. Instead, one ideally needs to understand the totality of the clinical picture of which a prospective memory deficit is one component. This is most likely to give the concordant evidence that is required to

characterize the central process. We will now illustrate this point by demonstrating that prospective failures in everyday life, even where they occur in the context of unimpaired intellect, retrospective memory, or problem-solving skills, usually do so in the context of a specific problem with behavioural organization of which prospective memory problems are one symptom.

Prospective memory failures as one symptom of a wider syndrome.

What would the everyday behaviour of a person with a severe acquired deficit of prospective memory look like? If every intended action that could not be enacted immediately was not carried out, or was executed out of sequence, or in response only to environmental prompts, then the result would be widespread behavioural disorganization, not just failure on prospective memory tests.

Perhaps the first description of such a person was reported seventy years ago. Penfield and Evans (1935) described the symptoms that Penfield's sister was experiencing after the removal of a right frontal glioma: "She had planned to get a simple supper for one guest and four members of her family. She looked forward to it with pleasure and had the whole day for preparation. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long continued effort alone".

This impairment in carrying out daily activities would not have been remarkable were it the case that the patient was suffering from serious disabilities in basic cognitive systems (e.g. classic dense amnesia, visuo-spatial/perceptual or agnosic problems, disorders of motor control and so forth). However this was not the case with Penfield and Evans' patient, nor with others which were soon reported (e.g. Brickner, 1936; Ackerly and Benton, 1947). These established, at least on the grounds of clinical observation alone, that this kind of behavioural disorganisation can be seen in the absence of these kinds of impairments.

However it was not until 50 years after Penfield and Evans's paper that an attempt was made to isolate the critical cognitive deficit underpinning this disorder. Eslinger and

Damasio (1985) described the case of EVR, who had undergone surgical removal of a large bilateral frontal meningioma. At the time of his operation EVR was a financial officer with a small company and a respected member of his community. He was married and the father of two children; his brothers and sisters considered him a role model and a natural leader. After the operation however, EVR lost his job, went bankrupt, was divorced by his wife, and moved in with his parents. He subsequently married a prostitute and was divorced again within two years. Extensive psychological evaluations found no deficit; in fact, he was superior or above average on most tests (e.g., Verbal IQ of 125; Performance IQ of 124; no difficulty on Wisconsin Card Sorting Test). He was also able to discuss intelligently matters such as the economy, foreign affairs, financial matters, or moral dilemmas. Despite these normal findings, EVR was often unable to make simple everyday decisions, such as which toothpaste to buy, what restaurant to go to, or what to wear. He would instead make endless comparisons and contrasts, often being completely unable to come to a decision at all. Further, Eslinger and Damasio report prospective memory problems: "...it was as if he forgot to remember short- and intermediate- term goals...."(1985, p.1737).

Eslinger and Damasio's paper was particularly important because it was the first convincing demonstration that this level of behavioural disorganisation could occur in the context of intact intellect, and intact performance on some tests traditionally thought to be sensitive to deficits in "frontal lobe" executive functions. However it was not possible to determine from this case alone whether the emotional and psychosocial problems that EVR displayed were necessarily linked to his prospective memory problems, or whether they were just associated deficits resulting from a large frontal lesion. Scientific progress on this front was limited at that time by two interlinked shortcomings: (1) No qualitative assessment had yet been undertaken of these kind of patients' everyday life problems, and (2) no laboratory task had been developed which a priori reflected these difficulties. Without (1) one could not begin to determine the range of behaviours under examination, or the characteristics of the situations which presented problems for the patients, and without (2) there was no simple "model of the world" which could form the basis for scientific investigation of the disorder at an information processing level.

Disorganisation in everyday life: From observation to experimentation.

Shallice and Burgess (1991) however addressed these issues. They presented three cases who had all suffered frontal lobe damage following traumatic brain injury. All three had no significant impairment on formal tests of perception, language and intelligence and two performed well on a variety of traditional tests of executive function. Indeed, one of these cases (AP) was probably the best example of the syndrome so far reported (this case was later called “NM” by Metzler & Parkin (2000)). AP had sustained sustained an open head injury in a road-traffic accident when he was in his early twenties. The injury caused a virtually complete removal of the rostral prefrontal cortex bilaterally plus damage to surrounding regions. On standard neuropsychological measures of intellectual functioning, memory, perception and even traditional tests of executive function, AP performed within the superior range.

This is not however to say that AP was unimpaired in other regards (Shallice and Burgess, 1991; Metzler and Parkin, 2000). The most noticeable of these in everyday life was a marked multitasking and prospective memory problem. This manifested itself as tardiness and disorganisation, the severity of which ensured that despite his excellent intellect and social skills, he never managed to make a return to work at the level he had enjoyed pre-morbidly. Shallice and Burgess (1991) invented two new tests of multitasking to assess these problems. The first of these tests, called the “Multiple Errands Test” was a real-life multitasking test carried out in shopping precinct. Participants have to complete a number of tasks, principally involving shopping in an unfamiliar shopping precinct, whilst following a set of rules (e.g. no shop should be entered other than to buy something). The tasks vary in terms of complexity (e.g. buy a small brown loaf vs. discover the exchange rate of the Euro yesterday), and there are a number of “hidden” problems in the tasks that have to be appreciated and the possible course of action evaluated (e.g. one items asks that participants write and send a postcard, yet they are given no pen, and although they cannot use anything not bought on the street to help them, they are also told that need to spend as little money as possible). In this way, the task is quite “open-ended” or “ill-structured” (i.e. there are many possible courses of action, and it is up to the individual to determine for themselves which one they will choose).

The second task that Shallice & Burgess invented was a more controlled experimental task (the “Six Element Test”). This required subjects to swap efficiently between 3 simple

subtasks, each divided into two sections within 15 minutes, whilst following some arbitrary rules (e.g. “you cannot do part A of a subtask followed immediately by part B of the same subtask). There are no cues as to when to switch tasks, and although a clock is present, it is covered, so that checking it has to be a deliberate action. Thus this paradigm has a strong component of voluntary time-based task switching, i.e. one form of prospective memory.

Despite their excellent general cognitive skills, AP and the other cases reported by Shallice and Burgess all performed these tasks below the 5% level compared with age- and IQ-matched controls. On the MET the subjects made a range of types of error, many of which could be interpreted as prospective memory failures. For instance they would find themselves having to go into the same shop more than once to buy items that could all have been be bought at one visit; not completing tasks that they had previously learnt that they needed to do; not remembering to come over to the experimenter and tell them what they had bought when leaving a shop (a pre-learnt task rule); or going outside the boundaries of the precinct (at the start of the test Ss are shown the boundaries and told not to cross them) (see Figure 1). They also made a range of social behaviour errors (e.g. leaving a shop without paying; offering sexual favours in lieu of payment). Shallice and Burgess (1991) rather inelegantly termed this kind of behavioural disorganization in the context of preserved intellect and other cognitive functions the “Strategy Application Disorder”.

FIGURE 1 HERE

It was not possible on the basis of Shallice and Burgess’s data however to speculate on the anatomical localization of the lesion critical for this pattern of deficit, since the patients had suffered large traumatic lesions. Two years later however, Goldstein et al (1993) described a case which began to suggest a possible locus. This 51-year old right-handed man (GN) had undergone a left frontal lobectomy 2.5 years earlier following the discovery of a frontal lobe tumour (mixed astrocytoma-oligodendroglioma). A 5cm resection of left frontal lobe from the frontal pole was undertaken. From the point of view of traditional neuropsychological tests, this surgery made little difference to his cognitive

abilities (e.g. WAIS-R VIQ 129, PIQ 111; story recall immediate 75-90th%ile, delayed 50-70th; Rey Osterreith delayed figure recall 80-90th%ile; Trail-making 70-75th%ile). However this did not reflect the change in his everyday competence. The patient had held a senior management position within an international company, but two years after surgery he had to take medical retirement because of increasing lethargy. He worked from home as a free-lance management consultant, but had difficulty making decisions, culminating in his taking two weeks to decide which slides to use for a work presentation, but never actually reaching a decision. He also experienced anger control difficulties.

Goldstein et al (1993) administered Shallice & Burgess's (1991) Multiple Errands Test. GN made significantly more errors than controls, being less efficient (e.g. having to return to a shop), breaking tasks rules (e.g. using a stamp that another customer gave him), misinterpreting tasks (e.g. sticking the stamp on the wrong card), as well as failing to complete some tasks altogether, reporting that he had known he had to do them but somehow "forgot" them. He also showed some "social rule" breaks. For instance, he had omitted to find out the price of tomatoes while earlier in the greengrocers, and realizing that he should not go back into the shop unless he was to buy something, he very conspicuously climbed onto the fruit display outside the shop and peered in the shop window.

This case, and others reported in the literature, show a remarkably similar pattern of neuropsychological test performance. Burgess (2000b) summarized the performance of 8 well-known cases: None of the cases had any language or visuoperceptual impairment and all scored within the superior range on tests of current intellectual functions. Four of the seven showed no impairment on any memory test. But most remarkably, two showed no impairment on a range of clinical executive function tests known to be sensitive to frontal lobe lesion. Moreover, no executive test has been failed by more than 2/8 cases. Most remarkably, two tasks have been administered to all the patients – the Wisconsin Card Sorting Test (WCST) and Verbal Fluency – and have been performed well by every case. This contrasts with the observation that all of the reported cases of "strategy application disorder" who have been given either the Multiple Errands or Six Element Tests have failed at least one of them.

The relation between prospective memory and long-term multitasking

The kind of multitasking described above critically requires prospective memory. "Multitasking" is a behavioural-level description that has a precise meaning in cognitive neuroscience. Burgess (2000a, b) describes 8 features of a situation that requires multitasking, the first five of which are axiomatic, plus a further three (6-8) that are usually true of everyday life multitasking situations:

1. Many tasks: A number of discrete and different tasks have to be completed.
2. Interleaving required: Performance on these tasks needs to be dovetailed in order to be time-effective.
3. One task at a time: Due to either cognitive or physical constraints, only one task can be performed at any one time.
4. Delayed intentions: The times for returns to task are not signalled directly by the situation.
5. No immediate feedback: there is no moment-by-moment performance feedback of the sort that participants in many laboratory experiments will receive. Typically, failures are not signalled at the time they occur.
6. Interruptions and unexpected outcomes: Unforeseen interruptions, sometimes of high priority will occasionally occur, and things will not always go as planned.
7. Differing task characteristics: tasks usually differ in terms of priority, difficulty and the length of time they will occupy.
8. Self-determined targets: People decide for themselves what constitutes adequate performance.

In this way, "multitasking" *may* be different, at least in some regards, in the information processing demands it makes from "multiple-task performance" which is where someone is performing several tasks simultaneously (or dual-tasking where there are two tasks, e.g. Baddeley et al, 1997). Prototypical dual- or multiple-task situations are air traffic control, or operating a computer whilst talking to someone on a telephone. There is little obvious prospective memory demand in e.g. dual-task situations since the retention interval over which an intention is to be maintained is typically so short. By contrast many real-life multitasking situations involve the co-ordination and dovetailing of many activities over longer time-scales (e.g. Alderman et al, 2003). These typically require one

to perform one particular task at a time (e.g. writing a scientific paper) whilst bearing in mind that other unrelated tasks have to be performed before completion of this task (e.g. collect the car from the workshop at 1pm) and often having to periodically check the state of something else (e.g. has the expected e-mail arrived yet?). In other words, whilst multitasking and multiple-task situations share characteristics 1 and 2 above (plus in some situations 5), only multitasking has characteristics 3 and 4. These characteristics necessitate the involvement of "prospective memory" (e.g. Kvavilashvilli and Ellis, 1996) or the carrying out of an intended action – in this case a task switch - after a delay. Indeed, we would argue that the most common example of a prospective memory action in everyday life is in the dovetailing of one's daily activities. Without this ability, one's behaviour would be very inefficient. For instance, one would have to always finish one task (e.g. cooking the vegetables for a meal) before starting another (e.g. other ingredients of the main meal), and operations that involve the integration of many sub-goals (e.g. visiting a number of different shops during one shopping trip) would be performed highly inefficiently.

What are the critical brain regions that support the prospective memory component of multitasking?

There is now some evidence that this prospective memory component of multitasking can be localized. The largest human group lesion study to date in this area was published by Burgess et al (2000), who examined a series of 60 acute neurological patients (approximately three-quarters of whom were suffering from brain tumors) and 60 age- and IQ-matched healthy controls on a multitasking test called the Greenwich Test. In this test, subjects are presented with three different simple tasks and told that they have to attempt at least some of each of the tasks in 10 minutes, while following a set of rules. One of these rules relates to all subtests ("in all three tasks, completing a red item will gain you more points than completing an item of any other colour") and there are four task-specific rules (e.g. "in the tangled lines test you must not mark the paper other than to write your answers down"). Thus this is a multitasking test where the majority of the variance in performance of the test comes from rule infractions rather than task-switching problems. The Greenwich Test was administered in a form that allowed consideration of the relative contributions of task rule learning and remembering,

planning, plan-following and remembering one's actions to overall multitasking performance. Specifically, before participants began the test, their ability to learn the task rules (by both spontaneous and cued recall) was measured; this measure was called "Learn". They were then asked how they intended to do the test, and a measure of the complexity and appropriateness of their plans was gained (a variable called "Plan"). This enabled us to look at whether their failures could be due to poor planning (see e.g. Kliegel et al, 2005). The participants then performed the task itself and by comparing what they did with what they had planned to do, a measure of "Plan Following" was made. Multitasking performance (the number of task switches minus the number of rule breaks) was referred to as the test "Score". After these stages were finished, subjects were asked to recollect their own actions by describing in detail what they had done (variable name: "Recount"). Finally, delayed memory for the task rules was examined ("Remember").

A basic finding was that this sort of procedure is sensitive to a range of cognitive problems – despite no differences between the controls and patients on measures of pre-morbid (NART) or current fluid intelligence (Raven's Advanced Progressive Matrices), the patients showed significant impairment on most of the variables (a similar finding is reported by Levine et al, 2000). At a more specific level however, lesions in different brain regions were associated with impairment at different stages in the multitasking procedure. Lesions to a large region of superior posterior medial cortex including the left posterior cingulate and forceps major gave deficits on all measures except planning. Remembering task contingencies after a delay was also affected by lesions in the region of the anterior cingulate. Critically, however, Burgess et al found that patients with left hemisphere rostral PFC lesions, when compared with patients with lesions elsewhere, showed a significant multitasking impairment (i.e. the variable "Score") despite no significant impairment on remembering task rules ("Remember" variable). Indeed, the left rostral prefrontal cases showed *no* significant impairment on any variable except the one reflecting multitasking performance. In other words, despite being able to learn the task rules, form a plan, remember their actions, and say what they should have done, they nevertheless did not do what they said that they intended to do.

This link between rostral PFC damage and the prospective memory component of multitasking accorded well with the lesion location of Goldstein et al's (1993) previous single-case. Moreover, two of the original three patients reported by Shallice and Burgess (1991) also had lesions affecting the rostral parts of the left frontal lobe. However a specific problem is presented by other findings. Thus one of Shallice and Burgess's (1991) cases had principally a right frontal lesion. Moreover Levine and colleagues (e.g. Levine et al, 1998; 1999; 2000) have repeatedly implicated right hemisphere lesions in poor performance on their multitasking test, the R-SAT. As Levine et al (2000) points out, these apparently conflicting results may be a result of the use of multitasking tests with differing characteristics: The Burgess et al (2000) study applied a test where the variable taken as an estimate of multitasking ability was based principally upon rule-following rather than task switching. But Levine's task (R-SAT) is more similar to Shallice & Burgess's original Six Element Test, in that the emphasis is upon voluntary time-based task switching rather than rule-following. So the lesion location differences could occur if task switching and rule-following are not equivalent in information-processing terms. This is certainly plausible with reference to the known characteristics of event- or time-based prospective memory (see e.g. Kvavilashvili and Ellis, 1996). Moreover, a recent group study of real-world multitasking in mixed aetiology neurological patients (Alderman et al, 2003) demonstrated a double-dissociation between rule-following and failures to initiate tasks. An alternative possibility however is that the difference between the findings of Levine's group and Burgess's may instead be due to the differing populations studied by them: Levine's finding are based principally on traumatic brain injury, but the Burgess et al (2000) study used acute circumscribed lesions (principally tumours).

A resolution to this apparent paradox was provided by a recent human group lesion study by Burgess, Veitch and Costello (submitted; reported in Burgess et al (2006). In this study, a new version of the Burgess et al (1996) Six Element Test (SET) of multitasking was given to sixty-nine acute neurological patients with circumscribed focal lesions and sixty healthy, using the administration framework of Burgess et al (2000). The SET differs from the Greenwich Test in that the multitasking score reflects mainly voluntary time-based switching rather than rule-following. Compared with other patients, those whose lesions involved the rostral prefrontal regions of the right hemisphere made significantly fewer voluntary task switches, attempted fewer subtasks, and spent far

longer on individual subtasks. They did not however make a larger number of rule-breaks (in contrast to the left rostral patients in the Burgess et al, 2000 study). As with the study of Burgess et al (2000), these multitasking deficits could not be attributed to deficits in general intellectual functioning, rule knowledge, planning, or retrospective memory.

Considering now the previous single case studies in the context of these group study findings, it is clear that there is a remarkably consistent finding of involvement of Area 10 in cases who have high-level disorganization in everyday life. For instance, in the 6 cases reviewed by Burgess (2000b) for whom good brain scan data was available, all of them had rostral PFC involvement of either the left or right hemispheres (or both). In addition to these cases, we might now also add the recent case of Bird et al (2004) who had suffered a rare form of stroke affecting the medial aspects of Area 10 bilaterally, and who failed the Six Element Test, despite passing some other executive tests (e.g. the WCST). It seems likely that prospective memory problems (and therefore multitasking ones) are just one indicator of the problems these unfortunate people experience.

Summary of evidence from human lesion studies.

Although it is a widespread belief that human lesion studies show that prospective memory must be supported in part by the frontal lobes (e.g. Cockburn, 1995) there is actually surprisingly little *direct* evidence (see e.g. Daum and Mayes, 2000). But what little evidence there is broadly supports this view. We have argued here that some of the critical components supported by the frontal lobes that contribute to prospective memory also contribute to other behaviours. In this way we expect that patients with even relatively isolated PM deficits will show concomitant deficits (i.e. will fail tests other than prospective memory ones, if the appropriate procedure is given). However there is now enough evidence to suggest that these concomitant deficits need *not* be in the domains of language, simple memory (e.g. recognition), perception, or even those abilities indexed by performance on many traditional executive function tests (e.g. Tower of London, Wisconsin Card Sorting Test). And there is enough evidence to suggest that, more specifically, rostral PFC plays a critical part in the ability to carry out what you intended to do after a delay, beyond that which can be explained by planning or retrospective memory. So what is the nature of this processing impairment that can

leave so many domains of cognition intact, but cause PM failures and also other symptoms (e.g. social behaviour abnormalities)?

The role of rostral PFC in prospective memory: Neuroimaging evidence.

Working on the basis that deficits in prospective memory were the core impairment in rostral patients with multitasking deficits, Burgess et al (2001) tested the link between rostral PFC and prospective memory using PET. Regional cerebral blood flow (rCBF) increases in lateral BA 10 were indeed found in prospective memory conditions relative to the ongoing task alone. This finding was in agreement with that of Okuda et al (1998) who also found increases in the left frontal pole. However Okuda et al were unable to determine whether this activation was associated with intention maintenance, target detection or the requirement for "dividing attention between the planned action and the routine activity" (p. 127). The Burgess et al (2001) study helped in this respect, by including a condition where Ss were told that an intention cue/target might appear, but none actually did. Critically, rCBF increases in lateral area 10 were also in this condition, i.e. where there is only the *expectation* of an intention cue, and a cue is never witnessed or responded to. Thus lateral BA 10 is more involved with the maintenance of an intention rather than cue recognition or intention execution.

A second PET study confirmed the role of lateral BA 10 in PM conditions, but also showed that *medial* BA 10 is more active in ongoing conditions than PM ones (Burgess et al, 2003). Furthermore, medial BA 10 was also more active (compared with PM conditions) in a simple attentional baseline condition where the S just responded as fast as possible to any change on the display.

The two Burgess et al PET studies had used a "conjunction" experimental design. This is where one investigates haemodynamic changes common to tasks which putatively stress the process of interest (Shallice, 1988) but where the other demands of the tasks are made quite different, by e.g. using spatial material for one, and verbal for the other. Accordingly, Burgess et al (2003) interpreted their results as suggesting that the functions supported by area 10 in prospective memory are "central" in the respect that they are material-inspecific, and unrelated to precise intention retrieval or cue

recognition demands. Instead, Burgess et al favoured an explanation in terms of one of the possibilities raised by Okuda et al (1998), that the rostral PFC rCBF changes were related to the attentional demands made by having to “bear in mind” an intention whilst performing an ongoing task.

Simons et al (2006) explicitly tested this hypothesis by measuring brain activity (using fMRI, and a conjunction of two different PM tasks: “Words” and “Shapes”) whilst manipulating the demands on either recognizing the appropriate context to act ("cue identification") or remembering the action to be performed ("intention retrieval"). In the “word task”, each trial consisted of two nouns presented next to each other in the middle of the screen, one of which was written in upper case and the other in lower case letters. For ongoing trials, participants were instructed to press the ‘4’ or the ‘6’ key on the keyboard depending on whether the left or the right word contained more letters. However, if the words belonged to the same semantic category, for example cow and horse, the ‘8’ key was to be pressed (“cue identification” PM condition). Furthermore, if the words were written in the same case, participants were required to count up the syllables of both words and press the ‘7’ key if the total was four or less, or the ‘9’ key if the total was higher than four (“intention retrieval” PM condition).

The stimuli in the “shape task” consisted of a 4×4 grid, in which a coloured triangle and a random other shape, such as a pentagon, were presented. For ongoing trials, participants were instructed to press the ‘4’ or ‘6’ keys depending on whether the shape which was not the triangle was presented to the left or the right of the triangle. However, if the two shapes were, spatially, a chess knight’s move away from each other, participants were instructed to press the ‘8’ key (“cue identification” PM condition). In addition, if the two shapes were of the same colour, participants were required to determine the number of sides of the shape other than the triangle, and press the ‘7’ key if this number was below or equal to five, and the ‘9’ key if this number was above five (“intention retrieval” PM condition).

A consistent pattern of hemodynamic changes was found in anterior prefrontal cortex (BA 10) across both types of task, and across both PM conditions (compared with the ongoing task): There was activation in lateral BA 10, which was accompanied by deactivation in medial BA 10. However, direct comparison of the “high intention retrieval

demand” with the “high cue recognition demand” PM conditions also revealed greater activation in lateral area 10 regions bilaterally in the intention retrieval condition. These regions were located somewhat more medially than those that showed activation common to both conditions (see Figure 2). Simons et al (2006) argue that the regions that were activated in both PM conditions may reflect the requirement in PM tasks for the biasing of attention between external events (e.g., identifying the cue amid distracting stimuli) and internal thought processes (i.e., maintaining the intention and remembering the intended actions). However it also seems from the comparison of the two PM conditions that there are some sub-regions of Area 10 which are more sensitive to particular PM task characteristics.

FIGURE 2 HERE

Further evidence for the specificity of some regions of area 10 comes from a recent paper by Okuda et al (submitted). In two positron emission tomography (PET) studies brain activity associated with time vs. event-based prospective memory (PM) tasks was examined. In the time-based condition of the first study young healthy volunteers were asked to make a response based on their self-estimation of the passage of time while engaged in an attention-demanding ongoing activity. In the time-based condition of the second study, participants had a clock available. Both studies showed activation differences in rostral PFC (principally BA 10) according to whether the task was time- or event-based.

In study one, subjects performed two prospective memory tasks (time, event) and a baseline task required the ongoing activity alone. The ongoing activity was a serial addition task. A digit, randomly selected from one to nine, was presented binaurally every 3 seconds and the subjects were required to add up the digits one by one and report the sum immediately after the presentation of each digit. The prospective response was to clench both hands. In the time-based task, the subjects were asked to make the prospective response once during the first 30 seconds, twice during the next 30 seconds, once during the third 30 seconds, and once during the last 30 seconds after the task started. In the event-based task, they were asked to make the prospective memory response when a cue stimulus (the number "7") was presented during the

ongoing activity. The cue stimulus was presented once during the first 30 seconds, twice during the next 30 seconds, once during the third 30 seconds, and once during the last 30 seconds. Okuda et al (submitted) found in this experiment that an area of left lateral superior rostral PFC (BA 9/10; peak coordinates x=-16, y=48, z=24) was more active during the time-based PM condition than during either the event-based PM one, or the ongoing task alone (see Figure 3).

Okuda et al's (submitted) second experiment used a conjunction design, looking at the activations common to two different PM tasks: "verbal" or "non-verbal", each presented in three conditions (Time PM; Event PM; Ongoing Task only). In the verbal tasks, the ongoing task required the participants, when presented with pairs of words, to make a same-different judgment based on the number of syllables in each word. For the ongoing task of the non-verbal conditions, participants were presented with a pair of rectangles and had to judge if the shapes were identical, regardless of their orientation. In the time PM conditions of each task, a clock was always presented at the center of the screen, which updated every 1 second to indicate current time from the start of the task. Ss were asked to press a button at every 1 minute after starting the task, and were told that they could use the information of the clock to help them. In the event PM conditions, Ss were asked to press a button whenever they encountered a cue stimulus, which was the word 'guitar' in the verbal tasks, or exact squares in the non-verbal tasks.

In contrast to the first study, a region of increased rCBF was found in left lateral rostral prefrontal cortex during the event-based PM conditions compared with the time-based conditions (Figure 3, panel c). This region was somewhat inferior within area 10 to that found in experiment 1 (Figure 3, panel a). Across both studies, rCBF in the rostro-medial prefrontal cortical regions increased during the time-based task and the ongoing-alone task as compared with the event-based task. These regions were more rostral, superior and closer to the midline than the medial BA 10 regions identified in experiment 1. (The aspect of exactly *where* within area 10 the activations occurred will become important in the discussion of the functions of area 10 below.) It is probably too early within our understanding both of the dynamics of prospective memory tasks, and of the functional architecture of area 10 to reach a full explanation of these results. However they do seem to suggest that brain activity in the rostral prefrontal cortex shows different patterns during the performance of time- and event-based prospective memory tasks.

Furthermore, they seem to suggest that subregions of area 10 are differentially involved in time-based tasks according to whether or not a clock is present as an aid to the passage of time. One possibility to explain this latter phenomenon, and which relates to the explanation of the Simons et al (2006) findings above, is that having a clock available increases the degree to which the participant attends to environmental stimuli rather than maintaining a continually updated, self-generated representation of the passage of time. In other words, it changes the relative amount of stimulus-*oriented* or stimulus-*independent* attending).

FIGURE 3 HERE

From prospective memory to the "gateway hypothesis" of area 10 function

In a series of experiments in our lab, we have investigated this possibility, i.e. that Area 10 is sensitive to differences in the degree to which cognition is stimulus-*oriented* or stimulus-*independent*. If brain area 10 supports a mechanism which enables us to either maintain thoughts in our head (i.e. *stimulus-independent cognition*) whilst doing something else, or switch between the thoughts in our head and attending to events in the environment (*stimulus-oriented attending*) then one would indeed expect that area 10 would play a central role in prospective memory. However it should not be the only ability that this region supports, since one can conceive of situations which require these psychological functions without having the characteristic of maintaining an intention over a delay period. So if we could design a paradigm which stresses this psychological mechanism but is *not* a PM task, and it activates Area 10 in a neuroimaging experiment, then this account is lent weight.

Accordingly, three functional neuroimaging experiments carried out in our laboratory investigated the evidence that area 10 is sensitive to differences in the source of the representations that are currently active in one's mind (for overviews see Burgess, Simons et al, 2005; Burgess, Gilbert et al, 2006). On this account, some thoughts are stimulus-independent, in the sense that they are self-generated (e.g. inventing a novel story) or are not prompted by things currently experienced witnessed (e.g. mind-

wandering). But some thoughts are directly provoked by, or oriented towards, stimuli that one can see (e.g. reading). In this way, the hypothesis was that Area 10 might act as an attentional “gateway” between inner mental life and the external world as experienced through the senses.

The first experiment to test this hypothesis was presented by Gilbert, Frith and Burgess (2005). They contrasted, using fMRI, the neural activation that occurs when people are performing tasks using stimuli presented on a display, with that which occurs when they are performing the same tasks “in their heads”. Medial Area 10 was found to be activated in the condition where people are using externally displayed stimuli (i.e. “stimulus-oriented attending”, SO) compared with when they are doing the same task in the absence of relevant stimuli (“stimulus-independent cognition”, SI). It also showed lateral BA 10 activation at the points where Ss switched between either condition, regardless of the direction of the switch (i.e. SO - > SI; SI -> SO). Thus the existence of a neural mechanism which arbitrates between stimulus-independent and –oriented thought received support, and a link between this mechanism and rostral PFC seemed a promising line of enquiry. A further fMRI study (Gilbert, Simons, Frith and Burgess, 2006) demonstrated *performance-related* activation (i.e. increased activation was associated with faster RTs) in medial Area 10 in simple reaction time conditions which did not require substantial stimulus processing. Thus the characteristation of medial rostral PFC as most active when an unusual degree of attention to external stimuli is required was supported.

Burgess et al then considered the possible role of *lateral* rostral PFC. The findings of patient’s problems with multitasking, and previous functional imaging studies of prospective memory (e.g. Burgess et al 2001; 2003) suggest a role for this sub-region of BA 10 in stimulus-independent cognition. However there are different forms of both stimulus-oriented and stimulus–independent attending. So Burgess, Dumontheil, Gilbert and Frith (submitted) examined the main forms of both in order to determine whether the lateral/medial distinction holds for all forms, and whether there is evidence for further functional specialisation within lateral or medial Area 10. Two quite different tasks were given under four conditions in a conjunction design. The conditions varied in the degree to which they made demands upon five attentional constructs, two of which were stimulus-oriented (vigilance, and stimulus attending) and three of which were stimulus-

independent in nature (mind-wandering; use of self-generated representations; and maintenance over a delay). Regardless of task, conditions stressing both of the stimulus-oriented attentional forms activated medial area 10, and all three that stressed stimulus-independent cognition activated lateral area 10 (see Figure 4). There was limited evidence for further functional specialisation. Thus the gateway hypothesis did indeed approximate area 10 findings across a range of conditions and tasks.

FIGURE 4 HERE

From the Gateway Hypothesis back to prospective memory

These results indicate that there may a general principle for the functional organisation of at least some parts of human brain area 10. This view receives further support from a meta-analysis conducted by Gilbert, Spengler et al (2006a). They analysed the reaction times (RTs) to paradigms from 104 PET/fMRI studies, yielding 133 independent contrasts. The tasks that had provoked these activations came from a wide range of functions, e.g. memory, mentalizing, perception, as well as prospective memory. A fascinating general principle emerged. Gilbert, Spengler et al (2006a) found that RTs to tasks which had provoked lateral area 10 activations tended to be slower than RTs in whatever control task had been used. The pattern occurred regardless of the type of task under study, and thus seems to be a general principle of area 10 neuroimaging findings. If lateral area 10 plays some part in effecting tasks which require the various forms of stimulus-independent cognition as argued here, then this pattern would be expected. This is because reaction times to tasks which require attending to stimuli *plus* some form of stimulus independent thought (e.g. performing an ongoing task whilst maintaining an intention, checking for PM cues etc.) will be longer, typically, than to tasks which only require the stimulus attending component (e.g. the ongoing task alone). This result also accounts for the consistent findings of rostral PFC activation in paradigms where there may be expected to be a novel degree of juxtaposition between stimulus-oriented and –independent thought, either induced intentionally by the task or because of spontaneous task-irrelevant thoughts (e.g. prospective memory and other multitask and switching paradigms, e.g. Braver and Bongiolatti, 2002; Burgess et al,

2001, 2003; Dreher et al, 2002; Koechlin et al, 1999, 2000; Okuda et al, 1998; Pollmann et al, 2001, 2004; or memory control processing, e.g. Fletcher and Henson, 2001; Herron et al, 2004; see Gilbert et al, 2006b for review).

However whilst there may be general principles for the organization of area 10 functions, this does not mean that there is not specialization within these parameters. Thus Gilbert et al (2006b) investigated, using the neuroimaging database described above, the location of activations within Area 10 according to the type of task being used. They found evidence for specialization of function within Area 10, with mentalizing tasks tending to provoke activations within caudal medial aspects of BA 10, episodic memory tasks (i.e. retrospective memory) being associated with lateral area 10 activations, and paradigms that required the co-ordination of two or more activities (including prospective memory) being associated with very rostral activations within area 10 (see Figure 5).

FIGURE 5 HERE

Conclusion

There is a gathering consensus amongst prospective memory researchers that the cognitive resources which underpin the episodic memory aspects of remembering a delayed intention are in some senses separable from those that support the control processing and attentional aspects of performance (e.g. Brandimonte and Passolunghi, 1994; Ellis, Kvavilashvili and Milne, 1999; Groot et al, 2002; Smith and Bayern, 2006; Marsh, Hicks and Cook, 2005; Maylor et al, 2002; McDaniel et al, 2004; Park et al, 1997; Sheeran, Webb and Gollwitzer, 2005; also chapters 2, 3, 4, 10, 11 and 13, this volume).On most conceptions, episodic (or “retrospective memory”) resources are used principally in e.g. maintenance of the intention trace; recognizing the prospective cue; remembering what it was that had to be performed, and so forth. By contrast, the “control”, “executive” or “attentional” resources are used to effect, e.g. active rehearsal of the intention; monitoring and maintaining an increased state of preparedness; dividing attention or switching between the ongoing task and intention rumination; determining

the allocation of attentional resources to either the ongoing task or to detecting the PM cue; and also strategic and motivational aspects of performance. Indeed, much recent research into the experimental psychology of prospective memory is concentrating upon the nature of these attentional resources and the demands made upon them by prospective memory tasks (e.g. Cohen et al, 2003; Nowinski and Dismukes, 2005; Einstein et al, 2005; McGann, Ellis and Milner, 2002; Hicks, Cook and Marsh, 2005; West, Krompinger and Bowry, 2005; see also chapters 2, 3, 4, 7, 8, 13 and 14, this volume). Moreover, it is in support of this resource that many researchers identify the role of frontal lobe structures (e.g. McDaniel et al, 1999).

However it seems that we can now be a little more precise perhaps than referring just to the “frontal lobes” in general. No doubt processes supported by many structures within the frontal lobes are utilized in the formulation and execution of delayed intentions. However one sub-region of the frontal lobes that seems on present evidence to play a particularly significant role is brain area 10 – the most anterior aspects of the frontal lobes. Patients with damage to this region show various forms of failing to carry out delayed intentions, and neuroimaging studies of prospective memory paradigms have consistently activated this region. But patients with damage to this region need not show retrospective memory problems, and neuroimaging studies of episodic memory have tended to associate area 10 with control or executive aspects of memory. Therefore it seems most plausible at present that the role that the processes that area 10 supports in prospective memory are bound up with the control or attentional components of PM functions.

As outlined above, one hypothesis that we have been pursuing is the role of area 10 in prospective memory is in the requirement that PM tasks make upon the active control of stimulus-independent vs. stimulus-oriented (or driven) cognition, and especially in the requirement to switch between these attentional modes. This is because actively maintaining an intention whilst performing some other task necessarily requires stimulus-independent thought (i.e. because you are thinking about something other than that which you are currently witnessing), and also stimulus-oriented cognition (i.e. processing stimuli in the performance of the ongoing task), and especially, the dovetailing of the two.

This explanation has the potential to explain many of the findings relating to performance of different forms of prospective memory task. For instance, one might think in these terms when hypothesizing about the processing differences made by (a) time-based PM tasks (when no clock is available) vs. event-based PM tasks, and (b) between time-based tasks where a clock is not available and the same task where a clock is available. In the former cases of both examples there is an increased need to maintain a *stimulus-independent* (SI) representation (e.g. a continually updated representation of the passage of time) and therefore considerable switching between this mode of attending and stimulus-oriented attending, as required by the ongoing task. By comparison, in the latter examples one might expect *relatively* increased attendance to information available in the environment, i.e. *stimulus-oriented* (SO) attending.

However we are at such an early stage of our understanding both of prospective memory and of the functions of area 10 that this must remain a hypothesis at present. In particular, whilst our experimental findings have emphasized a medial/lateral area 10 functional distinction, the results from our meta-analyses suggest that there are additional functional distinctions to be made in Area 10 along a rostral-caudal dimension, and that this may relate somehow to the varying demands that PM tasks make upon retrospective memory vs. executive control processing. Moreover, we have yet to discover how the processes supported by area 10 which we suggest are involved in prospective memory may also be used in the furtherance of other behaviours. For instance: (a) our lab has also shown substantial area 10 activations that are provoked by context memory paradigms, and these see to show anatomical overlap with some of those activated by both PM and SI/SO attentional switching paradigms (Simons, Gilbert et al, 2005; Simons, Owen et al, 2005), and (b) prospective memory failures do not seem to be the *only* symptom shown by patients with rostral PFC damage. Clearly we still have a great deal to learn. However, progress both in our understanding of the experimental and motivational psychology of prospective memory, and also in the neuroscience of prospective memory has been so rapid over the last 10 years that there must be considerable hope for our future understanding of this important human behaviour, and how the brain supports it. Moreover, it seems increasingly likely that progress in both fields will go hand-in-hand.

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FIGURE LEGENDS

Figure 1

Performance of a patient with rostral PFC damage on the Multiple Errands Test (Shallice and Burgess, 1991), and a typical control matched for age, sex, and estimated pre-morbid ability (NART). The patient took twice as long as the control yet failed to complete a number of tasks (the control completed them all). He also went out of bounds (boundary indicated by hatched line at end of street); entered shops more times than was needed; entered shops that were not necessary for the task, and made a number of task and social rule breaks. The patient was however able to repeat the task rules correctly both before and after the test.

Figure 2

Data from Simons, Schölvinck, Gilbert, Frith, and Burgess (2006) indicating that Cue Identification and Intention Retrieval components of prospective memory have a largely common neural basis in anterior prefrontal cortex (BA 10). Activations of principal interest are circled. Z coordinates are shown in top left corner of each axial image, and the inferior-superior location of the slices is indicated on the sagittal projection shown in panel (d). (a) Contrasting cue identification PM trials with ongoing trials, bilateral BA 10 activation (9 slice) and medial BA 10 deactivation (-6 slice) was observed. A highly similar pattern is shown in panel (b), the intention retrieval PM vs. ongoing contrast. Differences between conditions emerge in panel (c), the direct intention retrieval PM > cue identification PM contrast, with significantly greater activation in anterior prefrontal cortex bilaterally in the intention retrieval PM condition, and evidence of deactivation in medial anterior BA 10.

Figure 3

Areas of activation during time- and event-based prospective memory tasks according to Okuda et al (submitted). Activation foci, encircled with a white ring, were superimposed on horizontal sections of anatomical MRI of the standard brain. Panels *a* and *b* show greater activation during time-based task than during event-based task, where participants had to estimate timing for time-based prospective response (study 1). Panel *c* shows greater activation during event-based task than during time-based task, where a clock was available for time-based prospective response (study 2). Panels *d* and *e* show greater activation during time-based task than during event-based task in study 2. The top right panel shows the height level of each section (white lines) within the brain on a mid-sagittal section of the standard anatomical MRI.

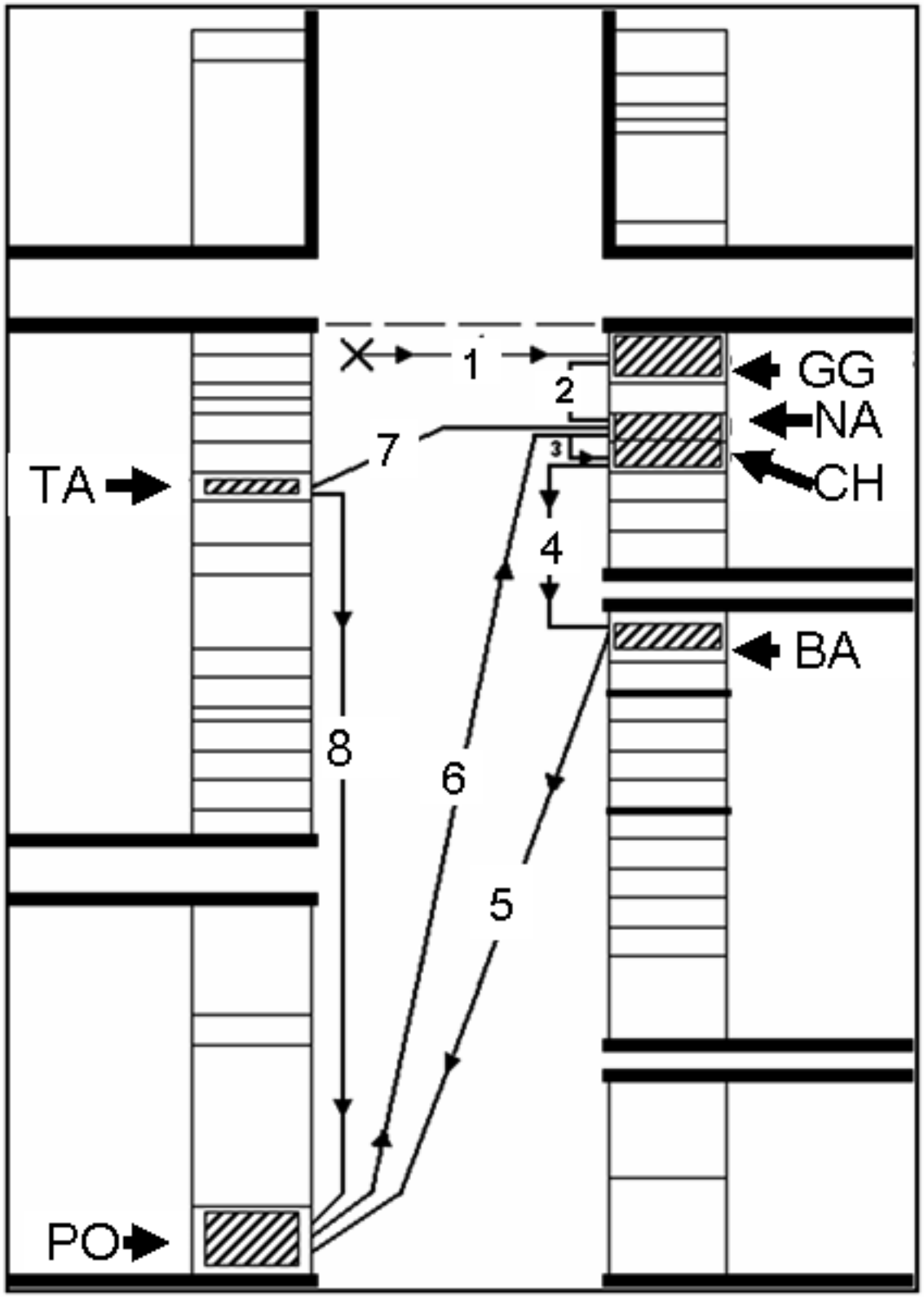
Figure 4

Results from Burgess, Dumontheil et al (submitted). On the left is shown a coronal slice of the brain at y = 60. The shades of grey represent the areas of activation, and overlaps between the activations, during 3 conditions (conditions 1, 2 and 4) which stressed stimulus-oriented cognition compared with a condition that made a high demand upon stimulus-independent thought (condition 3). So the darkest shaded regions, for instance, indicate that all three stimulus-oriented conditions activated this area: a large region of medial BA10. On the right is shown a coronal slice of the brain at y=49, demonstrating a second set of contrasts, and the overlaps between the areas revealed by them. The contrasts compare conditions 1, 3 and 4, which had a substantial stimulus-independent component, to condition 2, where attention is just maintained on stimulus oriented thoughts. Lateral BA 10 regions are revealed by these contrasts, and there is substantial overlap in the location of the activations demonstrated by them.

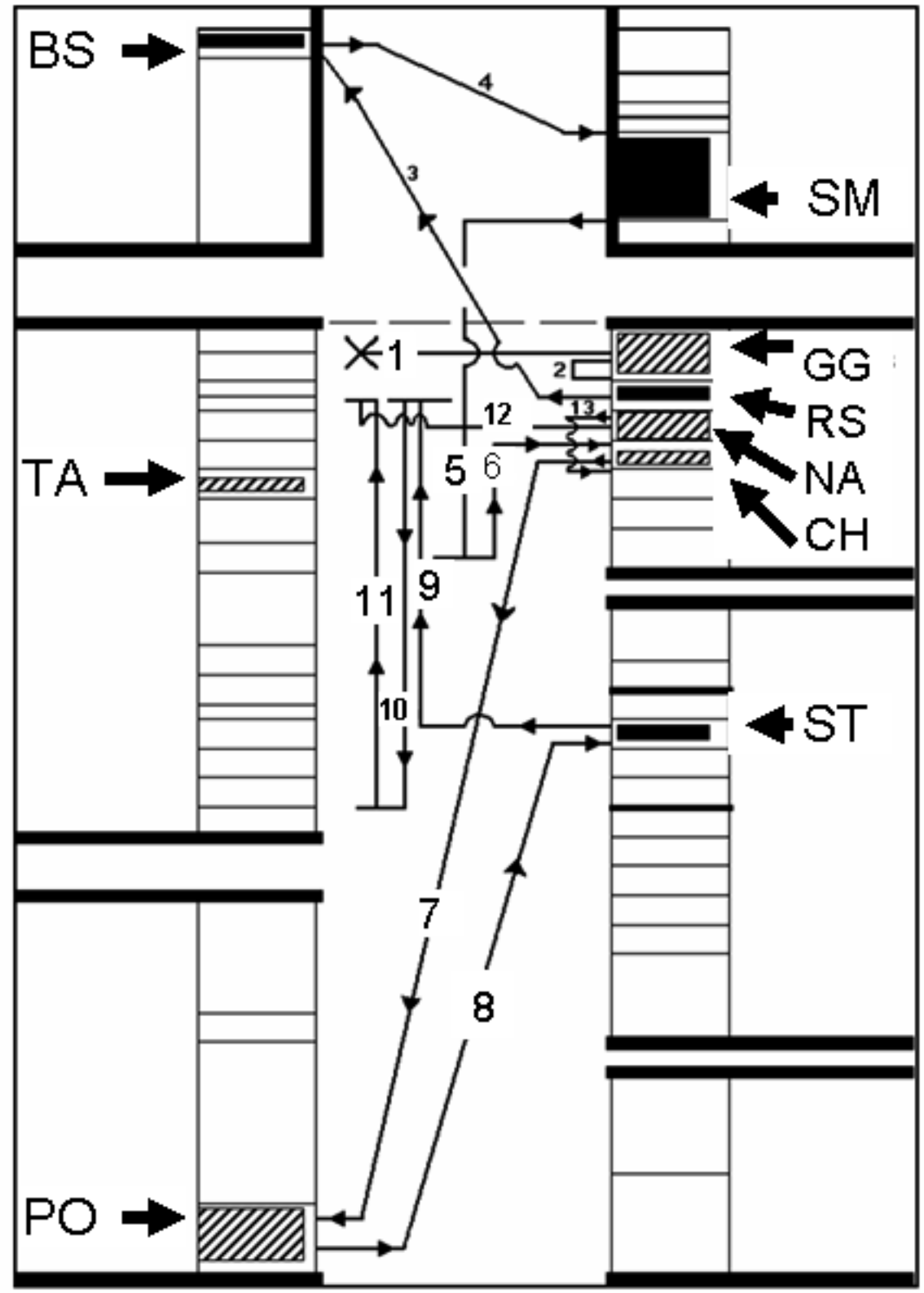
Figure 5

Results from the classification algorithm developed by Gilbert et al (2006b). This figure shows the predicted regions of activation for three types of task: those involving episodic retrieval (i.e. retrospective memory), “mentalizing” (e.g. theory of mind and other metacognitive judgements), and “multitasking” (any task involving the co-ordination of >1

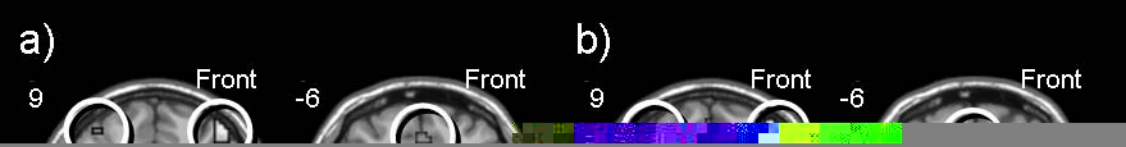
task, including prospective memory paradigms). Results are plotted on an axial slice of a normalized T1 weighted image (z =0). See text for details.

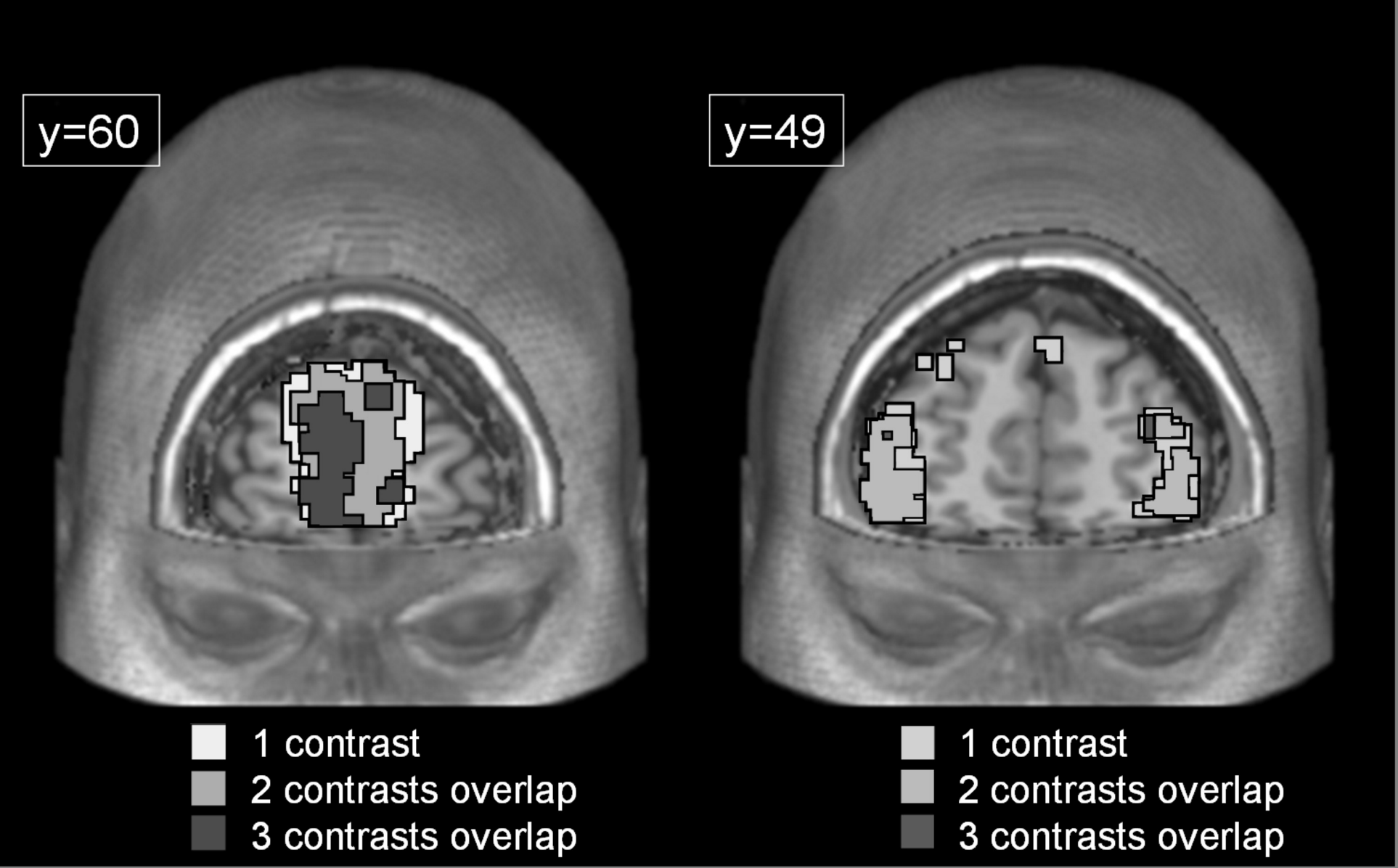


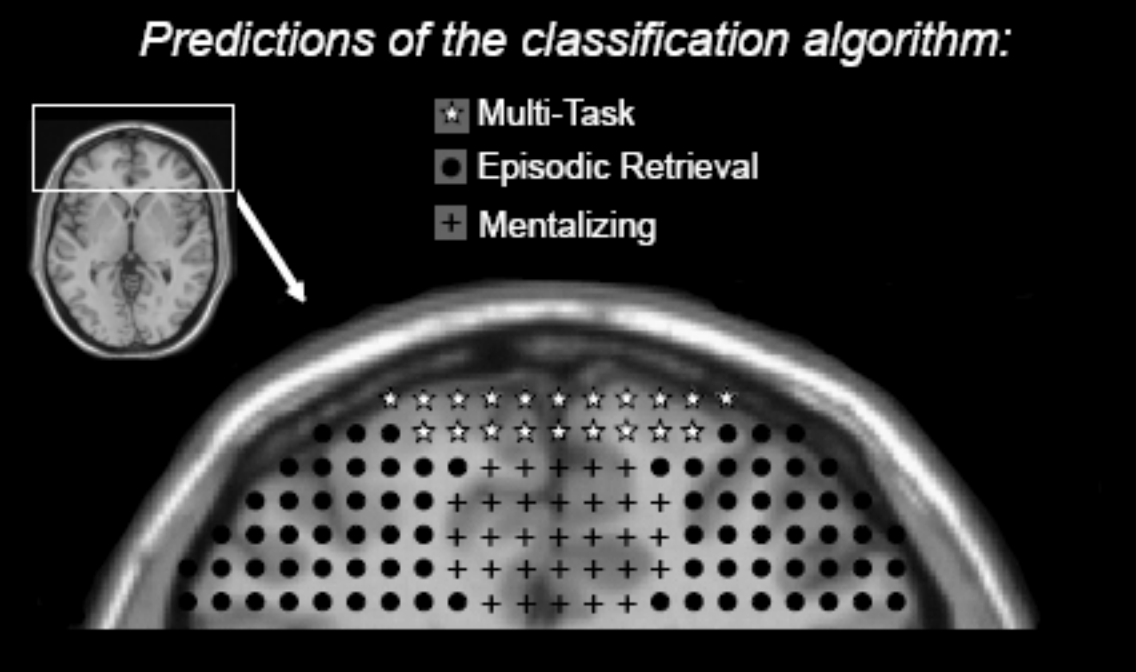
Matched Control



Person with Rostral PFC Lesion


a)
9
Front
-6
Front
b)
9
Front
-6
Front


y=60
y=49
1 contrast
2 contrasts overlap
3 contrasts overlap
1 contrast
2 contrasts overlap
3 contrasts overlap


Predictions of the classification algorithm:
Multi-Task
Episodic Retrieval
Mentalizing